Letters

Insulin Treatment for Type 2 Diabetes

To the Editor.—We are intrigued by the data of Dr Hayward and colleagues[1] on the treatment of type 2 diabetes by generalists, but we question their conclusions. They found mean hemoglobin A_{1c} (HbA_{1c}) levels in all patients to be 8%, better than in earlier studies. Sixteen percent of patients not taking insulin initially began insulin and had 0.9% lower HbA_{1c} levels a year later. Despite this improvement, 60% of these patients failed to reach an 8% (0.08) HbA_{1c} level that indicated acceptable control. Short-term costs of starting insulin included a few more visits and tests and a 4-fold increase in glucose self-testing.

The authors emphasize that insulin treatment was "rarely effective in achieving tight glycemic control." In contrast, we are impressed that the overall mean HbA_{1c} level was as good as 8% (0.08), reflecting more effective treatment than usual. Also, intervention trials[2,3] have shown that reducing HbA_{1c} levels by 1% should reduce many complications by 30% to 40%. This is a large effect, but the human and financial benefits would not easily be seen in just 1 year.

Moreover, the therapeutic tactics used during the study are already out-of-date. Beginning insulin with an evening injection while continuing oral agents is simple and effective. Three new kinds of oral agents that enhance the effectiveness of insulin are now available. We know from our own practices that a clear majority of patients, including those needing insulin, can achieve HbA_{1c} values below 8% (0.08). For example, Hellman and colleagues[4] tracked the health outcomes of all patients seen in their diabetes practice over a 14-year period. They found that patients who continued follow-up for at least 5 years had HbA_{1c} values averaging 7.3% (0.07) even before the new oral agents were available. When those who were severely ill at first contact were excluded, their patients had 60% less renal failure and 45% lower mortality than those not continuing individualized treatment beyond 5 years.

We fear this article's conclusions may be misinterpreted. The authors state that "given its modest effectiveness, patient inconvenience, and substantial increases in short-term resource use, simply encouraging primary care physicians to increase their use of insulin therapy seems a suboptimal strategy. . . ." Does this mean use of insulin should be discouraged, or rather, as we believe, should it be modernized and increased? Moreover, since resource utilization is part of its title, the study seems to compare costs and outcomes. But, with incomplete data on short-term costs and none on long-term costs, savings, and health benefits, a true cost-benefit analysis cannot be done. Even so, the accompanying Editorial was entitled "Controlling Type 2 Diabetes: Are the Benefits Worth the Costs?"[5] indicating that, regardless of the report's intentions, it raises questions of cost vs benefit that cannot be answered from the data.

More practical questions call for discussion. Why was the overall glucose control so good in this health care system? How can insulin use be improved in the primary care setting? What subgroups of patients benefit most from diabetes teams like Dr Hellman's? Sadly, generalized comments on the ineffectiveness of insulin may be enthusiastically quoted to justify short-term cost-cutting instead.

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1. Hayward RA, Manning WG, Kaplan SH, Wagner EH, Greenfield S. Starting insulin therapy in patients with type 2 diabetes: effectiveness, complications, and resource utilization. *JAMA*. 1997;278:1663-1669.
2. Diabetes Control and Complications Trial Research Group. The effect of intensive insulin treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977-986.
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To the Editor.—Dr Hayward and colleagues[1] refer to the relationship between HbA_{1c} and microvascular disease demonstrated by the Diabetes Control and Complications Trial Research Group as the basis for exploring effective strategies for improving glycemic control in individuals with type 2 diabetes.

One of the ways insulin achieves glycemic control is by facilitating the formation of triglyceride as evidenced by weight gain among the mostly lean, younger, insulin-dependent diabetes mellitus population of the Diabetes Control and Complications Trial.[2] Even if we achieve a lower incidence of microvascular disease by glycemic control through therapy that includes insulin, should we not be concerned about the association of macrovascular disease with higher lipid levels in the mostly obese, older type 2 diabetics?

We need a Diabetes Control and Complications Trial–type study in patients with type 2 diabetes not only to prove the effectiveness of therapy in terms of glycemic control but also to demonstrate that we are not substituting one complication for another. Managed care companies, who stand to gain the most financially, should consider funding such a study.

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1. Hayward RA, Manning WG, Kaplan SH, Wagner EH, Greenfield S. Starting insulin therapy in patients with type 2 diabetes: effectiveness, complications, and resource utilization. *JAMA*. 1997;278:1663-1669.
2. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977-986.

To the Editor.—The article by Dr Hayward and colleagues[1] found that the real-world effectiveness of instituting insulin therapy for patients with type 2 diabetes succeeded in lowering the HbA_{1c} levels by about 1% in the hands of the primary care clinicians involved in the study. I share their sentiments that achieving tight glycemic control is often a difficult and resource-consuming endeavor. Their conclusion that "insulin therapy was largely ineffective in achieving tight glycemic control" struck me as remarkable. Why blame the drug for the relative ineffectiveness? If used appropriately, insulin therapy can be associated with near normal glycemic control in type 2 diabetes, as seen in the

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Edited by Margaret A. Winker, MD, Senior Editor, and Phil B. Fontanarosa, MD, Senior Editor.

Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes.[2] The mean insulin dose of 55 U/d in the Hayward study suggests that their investigators were using a good drug ineffectively, rather than using an ineffective drug. Numerous studies have indicated that near normal glycemic control can be achieved in patients with type 2 diabetes by using insulin doses of 0.5 to 1.0 U/kg per day, which most often translates to greater than 100 U/d.[2,3]

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1. Hayward RA, Manning WG, Kaplan SH, Wagner EH, Greenfield S. Starting insulin therapy in patients with type 2 diabetes: effectiveness, complications, and resource utilization. *JAMA.* 1997;278:1663-1669.
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3. Henry RR, Gumbiner B, Ditzler T, et al. Intensive conventional insulin therapy for type II diabetes. *Diabetes Care.* 1993;16:21-31.

To the Editor.—We read with interest the report by Dr Hayward and colleagues[1] regarding the treatment of type 2 diabetes in a large staff-model health maintenance organization. However, several issues concern us. Most troublesome are conclusions drawn from comparisons between 2 groups of patients (insulin treated and non–insulin treated) that were not generated by randomization and that therefore may differ in ways other than insulin treatment. In fact, it is very likely that patients started on insulin by their physicians are different as a group than those not treated with insulin by those same physicians. Observations of differences in treatment effectiveness, complications, and resource utilization between these groups are necessarily affected by the underlying group differences.

Second, how much time did the primary care physicians spend with the patients? The most recent data on this point suggest that 68% of diabetes-related medical visits last less than 15 minutes and the average time for a physician visit for a general or family practice physician visit is 14.8 minutes.[2] Diabetes is a complicated chronic medical condition that in the best of circumstances takes enormous amounts of time, and in this nonacademic setting it is possible that the physicians actually spent less time than the national average. This is an important point when considering resource use, because the frequency of visits appears significantly higher than in other surveys. For example, in 1989, 60% of individuals in the United States with diabetes receiving insulin therapy had 6 or fewer visits per year.[2] The average number of visits for patients initiating insulin in the health maintenance organization was 12.6 per year (and in the year prior to insulin therapy was 9.7 per year).[1] Why is utilization so high for this population? It is possible that the cause for the disappointing results was too little time spent by the physicians with the patients and that insufficient time per visit resulted in greater utilization. We suggest that diabetes teams, with some of the care provided by diabetes clinical nurse specialists and nutritionists, seeing patients 4 to 6 times per year for 15 to 30 minutes, would provide better care at a reduced cost. Nonphysicians can manage very difficult patients receiving insulin therapy.[3]

We also disagree with the authors' assumption that the goal of insulin treatment in all of the study patients was "tight control," thus concluding that insulin was "rarely effective." For older patients, especially those with significant comorbidities, moderate glycemic control is a perfectly appropriate goal.[4] Since 50% of the study population was older than 65 years, we believe that it is misleading to classify all of the 60% of patients who ended the study with an HbA_{1c} level above 8% (0.08) as having received "ineffective insulin therapy."

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1. Hayward RA, Manning WG, Kaplan SH, Wagner EH, Greenfield S. Starting insulin therapy in patients with type 2 diabetes: effectiveness, complications, and resource utilization. *JAMA.* 1997;278:1663-1669.
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To the Editor.—Dr Hayward and colleagues[1] emphasize that therapy in type 2 diabetes, especially insulin therapy, was rarely effective in actual clinical practice in achieving tight glycemic control. Few patients receiving insulin therapy reached commonly proposed goals for near normalization of HbA_{1c} levels. While overall, 60% had HbA_{1c} levels of at least 8% (0.08), only 43% of the 690 patients treated with sulfonylureas and 18% of the 184 patients not receiving any hypoglycemic medication in this health maintenance organization had HbA_{1c} levels of at least 8% (0.08).

In our primary health care group practice, we evaluate our diabetes care based on intermediate outcome targets such as total glycated hemoglobin.[2] The mean glycated hemoglobin level of our 180 patients with type 2 diabetes, solely treated in primary care, was 5.2% (0.05; 95% confidence interval [CI], 4.9%-5.5%) in 1996. Of all patients with type 2 diabetes in our practice, 2% are treated by hospital-based physicians, so the possible referral bias will be minimal. Of all patients, 65% were treated with oral hypoglycemic medication (mean glycated hemoglobin, 5.2% [0.05]; 95% CI, 5.0%-5.5%) and 20% by diet therapy only (mean glycated hemoglobin, 4.3% [0.04]; 95% CI, 4.0%-4.7%). Fifteen percent of type 2 patients were treated with insulin therapy (mean glycated hemoglobin, 6.9% [0.07]; 95% CI, 6.4%-7.4%). Of the type 2 patients, 6.6% had a glycated hemoglobin level of at least 8% (0.08) in 1996, 0% of those receiving diet therapy only, 5% of those receiving oral hypoglycemic medication, and 22% of those receiving insulin therapy. Patients with type 2 diabetes taking oral hypoglycemic medication had 4.6 clinic contacts compared with 7.9 contacts for those using insulin. During 1996, 1 hypoglycemic grade III event was reported. The mean age of patients receiving insulin therapy was 64 years and for those not receiving insulin was 69 years.

Differences between the the Type II Diabetes Patient Outcomes Research Team Study population and our practice population with type 2 diabetes might be found in age and perhaps in body mass index, since in our studied population, the mean body mass index for those using insulin therapy was 30 kg/m^2 and for those not using insulin it was 28.

In addition to our observations, in a shared-care model de Sonnaville et al[3] recently demonstrated that implementation of structured care, including patient education and therapeutic advice, resulted in sustained good glycemic control with a mean HbA_{1c} level of 7% (0.07) with low risks of hypoglycemic events in the majority of 350 type 2 patients followed up for 2 years in 22 primary health care practices. In my opinion, there is no valid evidence to blame insulin or other treatment modalities for type 2 diabetes.

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1. Hayward RA, Manning WG, Kaplan SH, Wagner EH, Greenfield S. Starting insulin therapy in patients with type 2 diabetes: effectiveness, complications, and resource utilization. *JAMA.* 1997;278:1663-1669.
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To the Editor.—The report by Dr Hayward et al[1] and the Editorial by Dr Colwell[2] are important contributions that indicate that effective treatment of patients with type 2 diabetes is difficult and not easily achieved. The essence of this report is that the care provided did not enable patients to achieve the recommended American Diabetes Association guidelines for glycemic control.[2] Table 2 demonstrates that 19% did not have an HbA_{1c} level measured and only 32% of those who did achieved glucose control. However, the report omits important details. Who helped the patients acquire the necessary education, understanding, and practice to be responsible for their care? Insulin doses reported were low and significantly less than those (1.0 U/kg) adequate for control of type 2, insulin-resistant patients.[3] Yet these patients, at considerable cost (10-12 visits, more laboratory tests, more glucose test strips), probably fared better than those in the general population.

Why was the treatment reported in this study ineffective? Can effective treatment be done at an acceptable cost? Physicians, patients, and our reimbursement systems share the responsibility. Sustained effective treatment is difficult. Physicians are often poorly trained and without available support by skilled nurses and dietitians. Patients are unwilling participants and require coaching to assume this key role.

Diagnosis of the problem is easy.[1] What is needed are new, innovative approaches that are effective (defined as achieving normal glucose, lipid, blood pressure, and eye, kidney, and foot status) applicable to all populations at acceptable cost. Peters et al[4] reported the value of a team approach, with care provided mostly by nurses and dietitians.

At the University of California San Francisco-Fresno, we developed a cost-effective diabetes treatment model[5] with a team of highly skilled nurses and dietitians, with physician supervision. Our patients, unlike those described by Hayward et al,[1] were mostly Latino, of low socioeconomic status, and with low literacy in English or Spanish.

The program begins with 2 days of intensive education, understanding, and practice and frequent blood glucose testing with results publicly displayed. Of the 40% taking insulin, one third required a 30% to 50% increase in insulin dosage to reduce glucose values to less than 8.9 mmol/L (160 mg/dL). Continuing care is by a diabetes specialty team (4 visits per year) and the referring clinician. Effectiveness is indicated by quarterly HbA_{1c} measurements of 7.4%±1.7% (0.07±0.02) (preprogram, 10.1%±2.5% [0.10±0.03]), along with near normal triglyceride levels (1.69±1.18 mmol/L [150±105 mg/dL]) and blood pressure (<130/80 mm Hg). All patients have yearly foot and dilated eye examinations. The cost is $150 per patient per year (exclusive of laboratory tests, medications, and glucose test strips). Could this model work in a managed care setting such as in the Hayward et al[1] report? The patient needs both effective care (mostly by the patient, taught and encouraged by educators) and a caring primary care physician.

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1. Hayward RH, Manning WG, Kaplan SH, Wagner EH, Greenfield S. Starting insulin therapy in patients with type 2 diabetes: effectiveness, complications, and resource utilization. *JAMA.* 1997;278:1663-1669.
2. Colwell JA. Controlling type 2 diabetes: are the benefits worth the cost? *JAMA.* 1997;278:1700.
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5. Shipp JC, Hughes T, Fox E, Vargas L. A diabetes treatment program (DTP) with EUP: an effective and cost-effective model. *Diabetes.* 1996;45:148.

In Reply.—Our study found that "conventional insulin therapy" as managed by generalist physicians was very effective in achieving moderate glycemic control for patients who were previously in poor control but was relatively ineffective in achieving tight control in this setting. In our article, we discussed several possible explanations for this, none of which "blamed the drug." Our results also suggest that it is probably wrong to blame the physicians. There was no evidence that some physicians achieved better results than others, so they would all have to be equally inadequate. This seems unlikely, especially since they achieved levels of average glycemic control that were substantially better than those in most previous reports. Rather, we think it is most likely that for insulin therapy to achieve tight glycemic control for most patients, you will likely need very motivated patients, who are overrepresented in experimental trials, or will need to supply more support to physicians and patients to further aid the management of insulin beyond what can be achieved in 2 to 3 additional brief visits per year. As Drs Riddle and Karl point out, one possible implication of our results is that simpler, yet highly efficacious regimens (such as nocturnal insulin, daytime oral medications)[1] may be underused.

We feel the claim that the average insulin dose of 55 U/d, reported in our study, is low is overstated and that it is unlikely to explain the findings. First, most patients were receiving twice-daily injections and were having at least occasional insulin reactions. Also, in the Veterans Affairs study[1] cited by Dr Lenhard, most of the improvement in HbA_{1c} levels was achieved with an average dose of about 65 U/d. True, some additional improvement occurred when multiple daily injections and 133 U/d were used, but the majority of insulin's effectiveness can be achieved with doses in the range found in our study. Further, from a policy viewpoint, we are not as interested in what can be done in a laboratory with study volunteers followed up under strict protocol, but rather what benefits will be realized in usual practice settings.

Dr Poothullil's concern about how treatment affects macrovascular disease is important but beyond the scope of our study. A British study[2] may soon produce experimental evidence addressing this important and controversial issue.[3]

We certainly agree with the general tenor of these letters that one of the highest priorities in diabetes care is to find efficient approaches that will improve on conventional diabetes care, especially for high-risk patients.[4] The type of team or specialty approaches mentioned by the letters' authors are certainly promising. However, despite the fanfare and claims that often accompany such programs, there are very few rigorous controlled studies that quantify their effectiveness. Indeed, the most rigorous evaluations have not shown the dramatic benefits that the anecdotal reports would lead us to anticipate.[5] We know that motivated patients who receive regular follow-up do well in these programs. However, such patients may have done well in a variety of settings. We do not need more case reports about how selected patients do in someone's practice or program; we need more rigorous trials to evaluate their effectiveness for the typical mix of diabetics found in a community practice. Given the fiscal constraints of the current health care market, future studies must carefully consider the costs and benefits resulting from directing such programs to all people with diabetes vs targeting those at high risk of complications.[4]

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1. Abraira C, Colwell JA, Nuttall FQ, et al. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VA CSDM): results of the feasibility trial. *Diabetes Care*. 1995;18:1113-1123.
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In Reply.—Drs Riddle and Karl make some important points regarding the article by Dr Hayward and colleagues.[1] In my accompanying Editorial, I tried to emphasize many of the same points. Controlling type 2 diabetes according to new American Diabetes Association guidelines is more feasible now than it was at the time of Hayward's study (1990-1993), due primarily to the introduction of new oral agents and more physiologic strategies for using insulin. Of course, we need long-term estimates on costs, which are not yet available.

As pointed out in the Editorial, however, it is highly likely that an aggressive approach, not only directed at HbA_{1c} levels, but also with indicated use of other proven preventive strategies (ie, angiotensin-converting enzyme inhibitors, aspirin, lipid drugs), will materially improve lifestyles and lower morbidity and costs from end-stage vascular complications in people with diabetes.

Thus, it may be predicted that a multifactorial approach to controlling risk factors in diabetic patients will eventually provide benefits that are well worth the costs of care for this devastating disease.

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1. Hayward RH, Manning WG, Kaplan SH, Wagner EH, Greenfield S. Starting insulin therapy in patients with type 2 diabetes: effectiveness, complications, and resource utilization. *JAMA*. 1997;278:1663-1669.

Concerns About Run-in Periods in Randomized Trials

To the Editor.—Nobody would disagree with Dr Pablos-Méndez and colleagues[1] that nonadherence in a clinical trial adversely affects statistical efficiency.[2,3] We believe, however, that these authors do not adequately consider the impact of nonadherence on the validity of a randomized trial, and hence draw inappropriate inferences about generalizability. Since patients who do not comply obtain no benefit, nonadherence in a clinical trial will produce bias in the estimation of the true efficacy.[3-5] For this reason clinical trials use a variety of useful strategies, including a run-in period to identify and enroll subjects who will adhere. In the Physicians' Health Study,[6] adherence during the run-in was the strongest predictor of adherence during the trial so prerandomization exclusion of nonadherers greatly enhanced validity. A successful run-in period in a trial enhances validity, which is a prerequisite for generalizability.

Pablos-Méndez and colleagues conclude that a run-in period to screen for adherence will underestimate the adverse effects of a drug. This may or may not be the case as subjects must take drugs to experience adverse effects. Enrollment of adherent participants may be particularly important to identify adverse effects associated with long-term use.

Pablos-Méndez and colleagues also state that clinical trials that use a run-in period do not accurately predict adherence in clinical practice. Because participation in a clinical trial that is testing an unproven therapy differs so markedly from adherence to a proven therapy, accurate prediction of adherence in clinical practice often cannot be obtained from a trial, regardless of a run-in. Adequate informed consent requires that participants know that the value of the experimental treatments is unproven. Similarly, the principle of equipoise requires that investigators be uncertain about the value of alternative therapies. Individuals commonly participate in primary prevention trials for altruistic reasons. By contrast, once benefits of a therapy are proven, health care professionals and patients will have different attitudes about utilization and adherence. Hence, the observed adherence to a therapy being evaluated in a clinical trial may not be directly applicable to clinical practice.

Because of the limited generalizability of adherence in a clinical trial to clinical practice, the adjusted estimate derived by Pablos-Méndez and colleagues[1] from the results of the Physicians' Health Study must be considered speculative. For adherence-adjusted estimates based on such probability calculations, there are substantial limitations relative to the original intention-to-treat estimate of the benefits of aspirin obtained in this trial.[6]

We agree with Pablos-Méndez and colleagues that health care professionals in clinical practice, like investigators in clinical trials, have limited ability at the time a therapy is initiated to predict which patients will adhere. However, successful run-in periods in clinical trials demonstrate that observed adherence over a short period is a strong predictor of subsequent, long-term adherence. Improved estimates of the impact of adherence in clinical practice would be obtained by incorporating similar assessments of adherence. The important role of adherence in the assessment of any therapy, especially long term, should be assessed in actual clinical practice.

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1. Pablos-Méndez A, Barr RG, Shea S. Run-in periods in randomized trials: implications for the application of results in clinical practice. *JAMA*. 1998;279:222-225.
2. Lang JM, Buring JE, Rosner B, Cook N, Hennekens CH. Estimating the effect of the run-in on the power of the Physicians' Health Study. *Stat Med*. 1993;12:111-128.
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To the Editor.—A potential confounder not addressed by Dr Pablos-Méndez and colleagues[1] relates to the interpretation of the placebo response. There is no good evidence that the placebo response is consistent or linear.[2,3] In their discussion suggesting that run-in periods that screen for placebo response make for clear criteria, the trials reported assumed linearity and consistency of the placebo response.[4] This may allow for a clearer application of inclusion and exclusion criteria but may confound conclusions regarding placebo responders and treatment effect and, therefore, influence results in a positive or negative direction.

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1. Pablos-Méndez A, Barr RG, Shea S. Run-in periods in randomized trials: implications for the application of results in clinical practice. *JAMA*. 1998;279:222-225.
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To the Editor.—The article by Dr Pablos-Méndez and colleagues[1] on the external validity of randomized controlled trials with placebo run-in periods does not mention a serious potential ethical dilemma. What happens to the subject who responds well during the run-in single-blind placebo phase of, for example, a randomized controlled trial for treatment of depression or hypertension? Are subjects just informed that they responded to the placebo and not enrolled? Were patients in such trials, especially studies in which subjects are dropped if they respond to placebo, given proper informed consent? What exactly is the participant told before the trial and after being dropped? Does the informed consent in such trials include all "procedures to be followed" including the fact that there is a "deceptive" elimination period? Does the consent form describe the exact circumstances by which patients can be terminated without their consent? It is possible (or perhaps even likely) that some trials have informed consents that may not quite adhere to the *Federal Register*,[2] not to mention the Nuremberg Code and the Declaration of Helsinki.

In addition, the history of the run-in period to increase the efficiency of the randomized controlled trial is much older than the authors of this article apparently realize. The attempt to eliminate placebo responders goes back to some of the earliest double-blind randomized controlled trials. For example, Gold and colleagues[3] attempted a placebo run-in phase in their famous trial that began in 1932. The issue of detecting placebo responders[4] was an active research agenda in the early 1950s, and large adherence run-in periods were used as early as the late 1960s.[5,6]

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1. Pablos-Méndez A, Barr G, Shea S. Run-in periods in randomized trials: implications for the application of results in clinical practice. *JAMA.* 1998;279:222-225.
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In Reply.—Dr Glynn and colleagues point out that including nonadherers in a clinical trial may compromise the validity of an efficacy study; we would not take issue with this point of view. Our article was meant to call attention to the complexities of applying estimates of treatment effects derived from such studies directly to clinical practice, difficulties that are compounded when considering alternative interventions tested in trials without a run-in period. We agree that it is difficult to know whether using a placebo drug run-in period to exclude nonadherers will lead to underestimation or overestimation of the adverse effects of a drug in the randomized phase of a trial. However, the use of an active drug run-in period to exclude nonadherers will selectively exclude those who are nonadherent because of adverse effects. The result will be underestimation of the rate of adverse effects in the randomized phase compared with the unselected population expected in clinical practice.

We also agree with Glynn and colleagues that predicting adherence in clinical practice is difficult, and that clinical trials may not be helpful in this regard. Adherence during a clinical trial may be lower than in practice because of uncertain benefit, or may be higher because of measures such as reminders and monetary incentives. We do not propose the use of adherence-adjusted estimates. We offered an example to illustrate, first, that differences may be of clinical, not just theoretical, significance, and second, that the assumptions required are highly artificial, as noted by Dr Riley.

The interesting ethical issues raised by Dr Kaptchuk are beyond the scope of our article. We recognize that other variations of run-in periods occur as a design feature in clinical trials and hope for further consideration of the subject.

The widespread acceptance of run-in periods in clinical trials to exclude nonadherers, nonresponders, subjects with adverse effects, or placebo responders will add complexity to the secondary, comparative analyses of the results and their application in clinical practice. Many clinicians may not fully understand the distinction between an efficacy and an effectiveness study and how this distinction may influence the interpretation of clinical trial results. Clinicians also may not fully understand how the use of a run-in period may need to be taken into account in applying the trial's results to a patient. A major point of our article is that investigators who report such trials should address these issues explicitly in the publication of their results.

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SV40-Contaminated Poliovirus Vaccine and Childhood Cancer Risk

To the Editor.—In examining the carcinogenic effects of exposure to simian virus 40 (SV40)–contaminated poliovirus vaccine, Strickler et al[1] concluded that such exposure "was not associated with significantly increased rates of ependymomas and other brain cancers, osteosarcomas, or mesotheliomas." The expectation that the available data provided reliable incidence rates for a comparative analysis using Poisson regression techniques deserves reconsideration.

The Surveillance, Epidemiology, and End Results (SEER) database captures only tumors occurring during ages 26 to 41 years, 17 to 31 years, and 9 to 24 years in the childhood-exposed, infant-exposed, and unexposed cohorts, respectively, as defined by Strickler et al. Clearly, the ages for which tumor incidence is known for the entire childhood-exposed and unexposed cohort are incongruent. Poisson regression is a powerful statistical tool; however, negative conclusions drawn from a comparison of 2 or more regression models mathematically generated from incidence rates of very different age groups may represent a misuse of the method and, perhaps, an error in judgment. Since these cancers are highly correlated with age, statistical and clinical conclusions are best limited to age groups adequately represented in all comparison groups.

Acknowledging the small numbers of ependymomas in SEER, the authors conclude no increase in these rates related to exposure. The ependymoma rates were 0.17 of 100 000 and 0.11 of 100 000 for the childhood-exposed and unexposed cohorts, respectively. Ependymoma incidence peaks in the first decade of life; therefore, higher rates of these tumors were likely to have occurred in the exposed cohort during childhood and would not be captured in SEER.

Both SV40 exposure and cancer rates in the small, homogeneous state of Connecticut may not represent those of the entire United States. Other investigators[2] have reported the incidence of ependymal neoplasms in Connecticut children younger than 20 years increased after the mid-1950s. Given the evidence[3] suggesting potential perinatal transmission of SV40, cohorts born after 1963 could also be infected with SV40 and may have similar cancer risks. Increased cancer reporting over time could contribute to higher tumor rates in the unexposed cohort.

With 71 mesotheliomas, the authors report negative results, mentioning that the small case number and young age of the cohorts limits this analysis. In fact, only 2 mesotheliomas occurred in the unexposed cohort compared with 45 and 23 in the childhood-exposed and infancy-exposed groups. Mesothelioma in the youngest cohort (unexposed) would be unlikely, so the accurate study conclusion is that no conclusions can be drawn, rather than there was "no significant cohort effect."

Ignoring that poliovirus vaccines contained different amounts of SV40 further complicates the interpretation of these data, because SV40 carcinogenesis is dose related. The

SEER data indicate that SV40 should not directly lead to cancer; however, it is unlikely that SV40 per se causes cancer, because most, if not all, human carcinogens require additional factors for tumor development. Just as SV40 may render infected persons more susceptible to asbestos carcinogenicity,[4,5] SV40 infection may play a similar role in the development of disease among individuals exposed to other carcinogens.

The analysis by Strickler et al[1] provides no reliable evidence regarding the presence or absence of an increased cancer risk relative to SV40 exposure. The role of SV40 as a potential cofactor in carcinogenesis deserves to be investigated more carefully.

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1. Strickler HD, Rosenberg PS, Devesa SS, Hertal J, Fraumeni JF, Goedert JJ. Contamination of poliovirus vaccines with simian virus 40 (1955-1963) and subsequent cancer rates. *JAMA.* 1998;279:292-295.
2. Dohrmann GJ, Farwell JR, Flannery JT. Ependymomas and ependymoblastomas in children. *J Neurosurg.* 1976;45:273-283.
3. Heinonen OP, Shapiro S, Monson R, et al. Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. *Int J Epidemiol.* 1973;2:229-235.
4. Carbone M, Rizzo P, Grimley PM, et al. Simian virus-40 large-T antigen binds p53 in human mesothelioma. *Nat Med.* 1997;3:908-912.
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In Reply.—Our study examined essentially all available information on cancer rates in the United States relevant to the periods before, during, and after the widespread exposure of infants and children to SV40 through contaminated poliovirus vaccine (1955-1963). Incidence data were obtained from the SEER program, the principal source of cancer statistics for the nation, which began in 1973. Thus, for the birth cohorts injected with contaminated vaccine, surveillance had not started until these individuals were at least 10 years of age. To examine rates of cancer at younger ages, we studied national mortality statistics as well as incidence data from the Connecticut Tumor Registry, the only population-based cancer registry in the country that was well established at the time of the event.

In trying to determine the age intervals addressed by SEER, Dr Fisher appears to have made an error in subtraction. The infant-exposed cohort was covered by SEER from ages 10 through 37 years, the childhood-exposed cohort from ages 20 through 46 years, and the unexposed cohort from ages 3 through 29 years. Thus, the cohort exposed in infancy, the critical period of exposure in animal models, overlapped with the unexposed cohort for ages 10 through 29 years in SEER.

This age overlap was ideal for the evaluation of osteosarcomas, a tumor reported by Fisher's colleagues[1] at Loyola University to contain SV40 DNA. Although the incidence of osteosarcoma is highest during the teenage and young adult years, we found that risk was unrelated to birth cohort in our data. The suitability of our statistical analysis was demonstrated by the closeness of observed and modeled cancer rates, as shown in Figure 1 of our article. Incidence data from Connecticut confirmed there were no changes in osteosarcoma incidence related to the period of vaccine contamination in any age group.

To study ependymoma, a brain cancer that mainly affects children younger than 5 years, we examined data from Connecticut. Contrary to Fisher's assertion, the incidence of ependymoma showed no rise during or immediately following the period of vaccine contamination in children 0 to 4 years, 5 to 9 years, or 10 to 14 years of age (Figure 2 in our article). Fisher cites an earlier study of childhood brain cancer in Connecticut conducted in the 1970s, which did not properly control for age.[2] That study broadly defined *children* as individuals younger than 20 years and used the raw number of cancer cases without reference to the increasing infant population during the years of the baby boom.

Our findings are consistent with studies in other countries. In Germany, Geissler[3] found that ependymoma incidence was somewhat lower among 885 783 persons treated in the first year of life with SV40-contaminated vaccine, as compared with 891 321 individuals born shortly thereafter, based on 22 years of follow-up. In Sweden, Olin and Giesecke[4] observed no increase of ependymoma among children given contaminated vaccine. Olin and Giesecke[4] also confirmed our null results regarding osteosarcoma and mesothelioma. The Swedish data, like our own, are sparse for the investigation of mesothelioma, since the birth cohorts exposed to SV40-contaminated vaccine did not yet reach the peak age for this asbestos-related neoplasm. Mesothelioma incidence rates around the world have increased markedly over the past several decades, but predominantly among older individuals unlikely to have received SV40-contaminated vaccine. In Sweden, mesothelioma rates have shown increases similar to those observed in the United States, although adults in that country did not receive SV40-contaminated vaccine (Patrick Olin, MD, PhD, written communication, September 16, 1997).

The findings to date are unremarkable, but it is clear that further surveillance of exposed cohorts in the United States and other nations is needed to clarify the potential risks from SV40-contaminated poliovirus vaccine.

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2. Dohrmann GJ, Farwell JR, Flannery JT. Ependymomas and ependymoblastomas in children. *J Neurosurg.* 1976;45:273-283.
3. Geissler E. SV40 and human brain tumors. *Prog Med Virol.* 1990;37:211-222.
4. Olin P, Giesecke J. Potential exposure to SV40 in polio vaccines used in Sweden during 1957—no impact on cancer incidence rates 1960 to 1993. Presented at: International SV40 Workshop; January 1997; Bethesda, Md.

CORRECTIONS

Incorrect Data.—In the Original Contribution entitled "Effect of Vitamin E and Beta Carotene on the Incidence of Angina Pectoris: A Randomized, Double-blind, Controlled Trial," published in the March 6, 1996, issue of THE JOURNAL (1996;275:693-698), the authors recently discovered a computing error that affects the size of the study population and has a slight effect on the relative risk (RR) estimates of the 29 133 participants in the Alpha Tocopherol, Beta Carotene Cancer Prevention Study: 23 862 were free of coronary heart disease at baseline, and during follow-up 1920 new cases of angina pectoris were observed. Of these, 930 occurred among α-tocopherol–supplemented subjects and 990 among the non–α-tocopherol–supplemented subjects, with an RR for incident angina pectoris of 0.94 (95% confidence interval [CI], 0.86-1.02; P=.15); 980 among the beta carotene–supplemented subjects and 940 among non–beta carotene–supplemented subjects, RR, 1.04 (95% CI, 0.96-1.14; P=.34). Compared to those who received placebo, the RR for the incidence of angina was 0.98 (95% CI, 0.86-1.11; P=.70) for the α-tocopherol group; 1.09 (95% CI, 0.96-1.23; P=.19) for the beta carotene group; and 0.98 (95% CI, 0.86-1.11; P=.73) for the group that received α-tocopherol and beta carotene combined. The original conclusions remain unchanged.

Incorrect Table Footnote.—In chapter 17 of the Primer on Allergic and Immunologic Diseases entitled "Immunopathogenesis of Gastrointestinal and Hepatobiliary Diseases," published in the December 10, 1997, issue of THE JOURNAL (1997;278:1946-1955), an error occurred in Table 17-2 on page 1952. In the footnotes to the table, the expansion for the abbreviation AIH should have been autoimmune hepatitis.